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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,780	08/30/2001	Kevin P. Baker	P2548P1C10	2570

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	09/943,780	BAKER ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 18 January 2007 has been entered.

2. Claims 27-34 are pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections Maintained

Claim Rejections - 35 USC §§ 101, 112

4. Claims 27-34 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Applicants maintain that the specification (pg. 119) provides evidence that the PRO357 gene is amplified in tumors and that one of ordinary skill in the art would find it credible that PRO357 has a diagnostic utility. Applicants argue that it is more likely than not for amplified genes to have increased mRNA and protein levels because, in general, gene amplification increases mRNA expression and in turn, increased polypeptide levels. Applicants' arguments have been fully considered but they are not persuasive. Unlike the situations wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, or wherein an invention has only limited utility and is only operable in certain applications and therefore has some degree of utility sufficient for patentability, in the present situation Applicants have not provided any testing of PRO357 mRNA or PRO357 polypeptide expression. In the absence of any information on the role, activity

or expression of the PRO357 polypeptide in cancer, the examiner therefore considers the asserted utilities to not be specific and substantial because the skilled artisan would not know if or how PRO357 polypeptide expression changes in cancer. Applicants' utility standard would mandate only a showing that it is "not implausible" that the invention will work for its intended purpose. If mere plausibility were the test for how to use a claimed invention, Applicants could obtain patent rights to "inventions" based on a disclosure consisting of little more than guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor disclose how to use an invention rather than merely proposing an unproved hypothesis. As set forth in Brenner v. Manson:

> But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy."

There is a complete absence of data supporting the statements which set forth the desired results of the claimed invention and the countervailing evidence shows that the skilled artisan would not know if or how PRO357 mRNA or PRO357 polypeptide changes in tumors. The examiner concludes that Applicants' have failed to teach how to use the claimed invention.

Applicants argue that the first Polakis declaration (filed 10/20/05) shows that, in general, there is a correlation between mRNA levels and polypeptide levels. Applicants argue that the second Polakis declaration (filed 6/13/06) presents evidentiary evidence that enables the examiner to draw independent conclusions. Applicants remind the examiner that Office personnel must accept an opinion from a qualified expert. Applicants' arguments have been fully considered but they are not persuasive. The MPEP makes clear, "factual evidence is preferable to opinion testimony ... ." The MPEP also makes clear, "opinion" testimony is entitled to be considered, i.e., it is "admissible" in an ex parte proceeding. MPEP §716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must

be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things:
(1) The nature of the fact sought to be established.
(2) The strength of any opposing evidence.
(3) The interest of the expert in the outcome of the case.
(4) The presence or absence of factual support for the expert's opinion.
Unless an "expert" states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight.

The nature of the fact to be established is whether PRO357 polypeptide expression is elevated in tumors. The first and second Polakis declarations do not provide any data concerning PRO357 mRNA expression, PRO357 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO357 transcripts and PRO357 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the first and second Polakis declarations and now the Scott declaration (discussed below). Without any evidence of PRO357 mRNA or PRO357 polypeptide expression the first and second Polakis declarations are of no avail to Applicants.

The Ashkenazi declaration filed 11/6/2003 asserts that:

> "absence of gene product overexpression still provides significant information for cancer diagnosis and treatment." Paragraph 6.

Applicants are arguing that whatever the expression level and whatever the correlation, the PRO357 polypeptide is useful because skilled artisans could figure out for themselves what any observed experimental result might mean. The specification does not disclose anything regarding "more accurate tumor classification." The examiner does not agree that such a disclosure provides a "specific benefit in currently available

form" because the expression of all polynucleotides or polypeptides from a tumor sample can invariably be classified as either increased, decreased, non-existent, or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect or characterize the tumor. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific nor a substantial utility.

Applicant states that a Declaration under 37 CFR 1.132 by Dr. Randy Scott. The Declaration is not found in the file as of 11/20/06, however, a copy of this Declaration was filed 10/23/2006 in related Application No. 10/677,669. Applicant argues that Dr. Scott, an eminent researcher in this field, is of the opinion that mRNA levels correlate with protein levels. The Scott declaration under 37 CFR 1.132 filed 20 November 2006 is insufficient to overcome the rejection of claims 22-26 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

The nature of the fact to be established is whether PRO357 polypeptide expression is elevated in tumors. Like the first and second Polakis declarations, the Scott Declaration does not provide any data concerning PRO357 mRNA expression, PRO357 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO357 transcripts and PRO357 polypeptide expression in tumors because there are

examples of genes for which such a correlation does not exist, as evidenced by the first and second Polakis declarations and the Scott declaration, which states "Although there are some exceptions on an individual gene basis...". Without any evidence of PRO357 mRNA or PRO357 polypeptide expression the Scott and Polakis declarations are of no avail to Applicants.

The specification does not disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Therefore, the disclosure that PRO357 gene is amplified in tumor tissue (lung and colon) as compared to normal tissue does not impute a specific and substantial utility to the PRO357 polypeptide. Based on the present disclosure, one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Thus, the present disclosure is simply a starting point for further research and investigation into potential practical uses of the claimed polynucleotides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicants argue that the first and second Polakis declarations are further supported by Molecular Biology of the Cell, 3rd ed., Molecular Biology of the Cell, 4th ed., Genes VI, and as additionally supported by Zhigang and Meric, establish that there is a positive correlation between changes in mRNA levels and changes in the corresponding protein levels. Applicants' arguments have been fully considered but they are not persuasive.

Molecular Biology of the Cell, Genes VI, Zhigang, and Meric are acknowledged. However, Molecular Biology of the Cell, 3rd ed. acknowledges that "other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made" (page 453, last full paragraph). Molecular Biology of the Cell, 4th ed. acknowledges that the final level of protein depends upon the efficiency with which each of the many steps from DNA to protein is performed (page 363, last full paragraph and page 364, Figure 6-90). Genes VI acknowledges that "production of RNA cannot inevitably be equated with production of protein" (paragraph bridging pages 847-848). Molecular Biology of the Cell and Genes VI are consistent with the examiner's position that the skilled artisan would not know if or how PRO357 polypeptide expression would change in cancer and that the present application does not disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The examiner does not agree that Figure 6-3, page 302 of Molecular Biology of the Cell, 4th ed. illustrates a basic principle that there is a correlation between increased gene expression and increased protein expression. This figure only illustrates that different genes can be expressed with different efficiencies.

Regarding Zhigang, it is acknowledged that Zhigang presents data showing a high degree of correlation between PSCA protein and mRNA expression (page 4 of 7, right column, last sentence). However, exceptions were noted (paragraph bridging pages 3 of 7 and 4 of 7; page 4 of 7, left column, full paragraph 1) and, unlike Zhigang, Applicants have not provided any testing of PRO357 mRNA or PRO357 polypeptide expression. Zhigang does not provide any data concerning PRO357 mRNA expression, PRO357 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue and provides evidence that further experimentation would be required to determine such and the significance, if any. The fact that there may be a general correlation between mRNA and protein does not tell the skilled artisan if the reported PRO357 gene amplification is associated with a corresponding in crease in PRO357 polypeptide expression or what information would be conveyed.

Meric states that the "fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells" (page 971, right column, first paragraph of "Introduction"). However, the present specification does not provide any testing of the level PRO357 mRNA or PRO357 polypeptide expression. Applicants' specification does not detail the relationship between the reported PRO357 gene amplification and a change in PRO357 polypeptide expression. Therefore, the difference in PRO357 polypeptide expression between cancer cells and normal cells is unknown, and thus not exploitable. Meric also acknowledges that several alterations in translational control occur in cancer (page 971, Abstract) and that gene expression is quite complicated (page 971, right column, first paragraph of "Introduction"), suggesting that protein levels can be modulated independently of the level of mRNA. The fact that one of skill in the art can potentially exploit the differences in gene expression between cancer cells and normal cells does not tell the skilled artisan if the reported PRO357 gene amplification is associated with a corresponding in crease in PRO357 polypeptide expression.

No information is provided in the gene amplification data regarding level of expression, activity, or role in cancer of the PRO357 polypeptide.

According to M.P.E.P. 2107.01 [R-3]:

> Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Similarly, Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered.

Neither the first nor the second Polakis declarations provides any facts regarding PRO357 polypeptide expression.

Pennica (Proc Natl Acad Sci U S A. 1998 Dec 8;95(25):14717-22, of record 6/11/2003) shows:

> *WISP-1* genomic DNA was amplified in colon cancer cell lines and in human colon tumors and its RNA overexpressed (2- to >30-fold) in 84% of

> the tumors examined compared with patient-matched normal mucosa. In contrast, *WISP-2* ... DNA was amplified, but RNA expression was reduced (2- to >30-fold) in 79% of the tumors. Abstract.

This is evidence that DNA amplification is not always associated with overexpression of the gene product and that the asserted diagnostic utility of the PRO357 polypeptide would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

Orntoft (Mol Cell Proteomics. 2002 Jan;1(1):37-45, submitted with response filed 11/10/2004) discloses that:

> "Gain and loss of chromosomal material is characteristic of bladder cancer, as well as malignant transformation in general. The consequences of these changes at both the transcription and translation levels is at present unknown partly because of technical limitations." Page 37, Abstract.

In addition, within the areas of gene amplification Orntoft observed genes whose expression was up-regulated, down regulated, or unchanged.

Hyman (Cancer Res. 2002 Nov 1;62(21):6240-5, submitted with response filed 11/10/2004) discloses that:

> "Besides amplifications of known oncogenes, over 20 recurrent regions of DNA amplification have been mapped in breast cancer by CGH ... . However, these amplicons are often large and poorly defined, and their impact on gene expression remains unknown." Page 6240, paragraph bridging left and right columns.

In addition, Hyman found that up to 44% of the highly amplified transcripts were overexpressed. "Up to 44%" does not translate into "more likely than not."

Pollack (Proc Natl Acad Sci U S A. 2002 Oct 1;99(20):12963-8, submitted with response filed 11/10/2004) discloses that:

> "An unresolved question is the extent to which the widespread DNA copy number changes that we and others have identified in breast tumors alter expression of genes within involved regions." Page 12963, paragraph bridging left and right columns.

In addition, it is acknowledged that Pollack found that 62% of highly amplified genes show moderately or highly elevated expression. However, it must also be acknowledged that 38% of highly amplified genes did not show moderately or highly elevated expression.

Godbout (J Biol Chem. 1998 Aug 14;273(33):21161-21168, IDS filed 11/20/2006) discloses that:

> Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified. Abstract.
>
> It is generally accepted that co-amplified genes are not overexpressed unless they provide a selective growth advantage to the cell. For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed. Similarly, three genes mapping to 12q13-14 (CDK4, SAS, and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GLI, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas. The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons. Page 21167, right column, full paragraph 1.

Pennica, Orntoft, Hyman, Pollack, and Godbout are evidence that the skilled artisan would not know if or how expression of PRO357 mRNA, the PRO357 polypeptide, or any of the other claimed polypeptides, would change in cancer.

Neither the specification nor any of Applicants' arguments, exhibits, declarations, asserted dogma, or other evidence provide any facts disclosing if or how PRO357 mRNA or PRO357 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a alleged general correlation between gene amplification and mRNA expression and extrapolate this general correlation to another general correlation between mRNA expression and expression of the encoded protein to argue that it is more likely than not that PRO357 polypeptide expression is elevated. Without any evidence of the expression of PRO357 mRNA or PRO357 polypeptide expression this argument is of no

avail to Applicants. Applicant must provide substantial evidence of an alleged diagnostic utility unless a skilled artisan would accept such an allegation as obviously correct. In present case, Pennica, Orntoft, Hyman, Pollack, and Godbout support the conclusion that skilled artisan would not accept such an allegation as obviously correct. Showing that it is "not implausible" that invention will work for its intended purpose is not sufficient to meet utility and enablement requirements.

Applicants are not being asked to prove the asserted diagnostic utility either as a matter of statistical certainty or beyond a reasonable doubt. Rather, the fact to be established is whether there is a change in PRO357 polypeptide expression in tumors. The specification does not establish if the disclosed PRO357 gene amplification is one of those cases where there is a correlation between gene amplification and polypeptide expression. Applicants have not provided any testing of PRO357 mRNA expression or PRO357 polypeptide expression. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO357 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO357 polypeptide, the specification does not provide some immediate benefit to the public for the PRO357 polypeptide. None of Applicants' exhibits, arguments or declarations establish if or how expression of PRO357 mRNA, the PRO357 polypeptide, or any of the other claimed polypeptides, changes in tumor tissue as compared to normal tissue. Instead, Applicants merely propose a utility that is "not implausible," relying on a general correlation gene amplification and mRNA expression extrapolated to another general correlation between mRNA expression and expression of the encoded protein without any evidence of the PRO357 mRNA or PRO357 polypeptide expression. See, e.g., Brenner, 383 U.S. at 534, 148 USPQ at 695 (An invention does not have utility sufficient to satisfy § 101 until it is "refined and developed" to the point of providing a specific benefit in currently available form.). Based on the present disclosure, one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Thus, the present disclosure is simply a starting point for further

research and investigation into potential practical uses of the claimed PRO357 polypeptide. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicants' arguments, exhibits and declarations only show that it is not implausible that invention will work for its intended purpose. In view of the countervailing evidence, Applicants' arguments, exhibits and declarations are insufficient to meet the utility requirement because they are insubstantial evidence that expression of the PRO357 polypeptide changes in a manner that corresponds to the reported PRO357 gene amplification.

Applicants submit additional references (Ids filed 11/20/06) and refer to previously submitted references (i.e., Pollack, Ornoft, Hyman, Bermont, Varis, and Hu filed 11/10/2004; and Paotti, Walmer, Janssens, Hahnel, Kammori, Bea, Maruyama and Futcher, filed 6/13/2006) to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide. However, none of these exhibits provide any facts concerning PRO357 gene amplification, PRO357 mRNA expression, or PRO357 polypeptide expression, or the correlation between them, in normal tissue and tumor tissue. The exhibits do not provide any data concerning PRO357 mRNA expression, PRO357 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. The fact that there may be a commonly understood general rule or dogma concerning gene amplification, mRNA expression, and polypeptide expression does not establish the correlation between PRO357 gene amplification and PRO357 polypeptide expression because there are examples of genes for which such a correlation does not exist, as

evidenced by Pennica, Orntoft, Hyman, Pollack, Godbout, and the first and second Polakis declarations. As indicated previously, Applicants have not provided any testing of PRO357 polypeptide abundance. It is unknown if the reported PRO357 gene amplification is associated with a corresponding change in PRO357 polypeptide expression.

Regarding applicants' previous submission of the art of Bea, Bea (Cancer Res. 2001 Mar 15;61(6):2409-12, submitted with the response filed 6/13/2006) also teaches that:

> However, the possible implication of the *BMI-1* gene in these alterations and its role in the pathogenesis of human tumors is not known. The aim of this study was to analyze the possible *BMI-1* gene alterations and expression in a large series of human neoplasms and to determine the relationship with *INK4a/ARF* locus aberrations. Page 2409, paragraph bridging left and right columns.

Bea teaches that prior to testing BMI-1 protein expression, the affect of *BMI-1* gene amplification on BMI-1 protein expression is unknown. Therefore, Bea is evidence that a skilled artisan would not know if the reported PRO357 gene amplification is associated with a corresponding change in PRO357 polypeptide expression.

Bea also teaches that:

> *BMI-1* is considered an oncogene belonging to the Polycomb group family of genes. These proteins mainly act as transcriptional regulators, controlling specific target genes involved in development, cell differentiation, proliferation, and senescence. Page 2411, paragraph bridging left and right columns.

There is no evidence of record that the PRO357 polypeptide is an oncogene or that confers a selective growth advantage on tumor cells. The examiner disagrees with applicants' assertion that 'the four MCLs with gene amplification of *BMI-1* "showed significantly higher levels of ... protein expression' because "BMI-1 protein expression was examined by Western blot in ... [only] two cases with *BMI-1* gene amplification" (page 2410, paragraph bridging left and right columns).

Applicants argue that Godbout supports applicants' assertion that gene amplification is associated with increased mRNA and protein expression. Applicant only cited the abstract of Godbout, the examiner is citing the entire reference. Applicants'

arguments have been fully considered but they are not persuasive. Godbout discloses that:

> Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified. Abstract.
>
> It is generally accepted that co-amplified genes are not overexpressed unless they provide a selective growth advantage to the cell. For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed. Similarly, three genes mapping to 12q13-14 (CDK4, SAS, and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GLI, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas. The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons. Page 21167, right column, full paragraph 1.

However, there is no evidence of record that the PRO357 polypeptide is an oncogene or that confers a selective growth advantage on tumor cells.

Applicants' summary is acknowledged. Applicants are not being asked to prove the asserted diagnostic utility either as a matter of statistical certainty or beyond a reasonable doubt. Rather, the fact to be established is whether there is a change in PRO357 polypeptide expression in tumors. The specification does not establish if the disclosed PRO357 gene amplification is one of those cases where there is a correlation between gene amplification and polypeptide expression. Applicants have not provided any testing of PRO357 mRNA expression or PRO357 polypeptide expression. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO357 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO357 polypeptide, the specification does not provide some immediate benefit to the public for the PRO357 polypeptide. None of Applicants' exhibits, arguments or declarations establish if or how expression of PRO357 mRNA, the PRO357 polypeptide, or any of the other claimed polypeptides, changes in tumor tissue as compared to normal tissue. Instead, Applicants merely

propose a utility that is "not implausible," relying on a general correlation gene amplification and mRNA expression extrapolated to another general correlation between mRNA expression and expression of the encoded protein without any evidence of the PRO357 mRNA or PRO357 polypeptide expression. See, e.g., Brenner, 383 U.S. at 534, 148 USPQ at 695 (An invention does not have utility sufficient to satisfy § 101 until it is "refined and developed" to the point of providing a specific benefit in currently available form.). Based on the present disclosure, one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Thus, the present disclosure is simply a starting point for further research and investigation into potential practical uses of the claimed polynucleotides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

5. Claims 27-34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant's arguments have been fully considered but they are not persuasive. As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a

matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

6. The rejection of claims 27-34 under 35 U.S.C. 102(b) as being anticipated by Bostein et al (WO 99/35170, published 7/15/1999) is maintained.

Applicants' argue that the present application is entitled to the filing date of priority application 60/113,296, i.e., 12/22/1998, which discloses the PRO357 polypeptide and amino acid sequence as well as the gene amplification experiment described in Example 28 of the present specification is described in Example 2 of the '296 application. According to applicant, for the reasons discussed above, description of the gene amplification in the '296 application satisfies the utility and enablement requirements for the PRO357 polypeptide. This has been fully considered but is not found persuasive for the following reasons.

Under 35 U.S.C. 120, the claims in a U.S. application are entitled to the benefit of the filing date of an earlier filed U.S. application if the subject matter of the claim is disclosed in the manner provided by 35 U.S.C. 112, first paragraph in the earlier filed application. Under 35 U.S.C. 119 (a) or (e), the claims in a U.S. application are entitled to the benefit of a foreign priority date or the filing date of a provisional application if the corresponding foreign application or provisional application supports the claims in the manner required by 35 U.S.C. 112, first paragraph. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph.

Therefore, the claims are not entitled to the benefit of the filing date of the earlier filed applications because the subject matter of the present claims is not disclosed in the manner provided by 35 U.S.C. 112, first paragraph, in the earlier filed applications

for the reasons set forth above in the rejections. Accordingly, the effective filing date for the claimed invention is 8/30/2001, which is the filing date of the instant application.

Conclusion

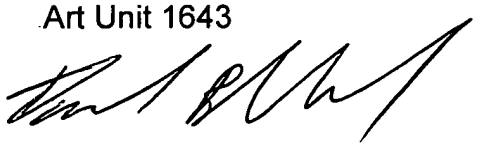
7. No claims are allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Blanchard
Patent Examiner
Art Unit 1643



DB
March 2, 2007